The Role of Hyaluronic Acid in Structuring the Bone Marrow Hematopoietic Niche

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The fate of hematopoietic stem cells is determined by microenvironmental niches [1]. Adhesion molecules and their ligands play a key role in the regulation of the hematopoiesis-supportive function of the microenvironmental niche [2]. The family of CD44 adhesion molecules comprises a large number of alternatively spliced glycoproteins. The major ligand for CD44 hyaluronic acid (HA) is present in bone marrow, where it participates in extracellular matrix assembly [3].

To unravel the role of HA in the regulation of hematopoiesis, long-term bone marrow cultures (LTBMC) were treated with a panel of defined-size HA polymers. While low molecular weight HA (LMW HA) inhibited both the formation of cobblestone areas within the adherent layer and the production of non-adherent cells in LTBMC, high molecular weight HA (HMW HA) stimulated hematopoiesis in LTBMC. HMW HA also improves bone marrow hematopoiesis after 5-FU in mice. Recovery of peripheral blood cells was facilitated and correlated with enhanced hematopoietic activity in the bone marrow. HA binds to marrow macrophages that exhibit surface expression of CD44 isoforms resulting in the cytoskeleton rearrangement, activation of signal transduction cascades, and up-regulation of IL-6 and IL-1 production. Gene expression profiling, using Affymetrix chip technology, allowed us to identify genes differentially expressed in the bone marrow cells exposed to HA vs. control, including genes that may mediate hematopoietic stem cell proliferation and self-renewal, suggesting the essential role of the CD44/HA pathway in the regulation of hematopoiesis [4-7].

Based on our results, we hypothesize that biological effects of HA on HSC–niche cross-talk are determined by the HA size. Specifically, while HMW HA provides signals supporting the retention of HSC within the niche, LMW HA initiates disruption of SDF-1/CXCR4, VCAM-1/VLA-4, and c-kit/SCF pathways resulting in HSC detachment. The experiments are designed with a view to investigate the function of defined-size synthetic HA polymers in the regulation of HSC fate in normal and chemotherapeutically stressed bone marrow. We are planning to test the hypothesis that in contrast to HMW HA, LMW HA polymers increase production and/or activation of MMP-9, which in turn degrades the HSC retention signals within the niche. These disruptions contribute in the detachment of HSC from the niche. We also hypothesize that while LMW HA is internalized via CD44, HMW HA remains on the cell surface providing receptor-mediated signaling. By using CD44 specific HA-binding blocking antibodies and specific downstream inhibitors of the CD44 pathway, we plan to address the role of CD44 in mediating HA-induced changes.

Overall, these studies will elucidate the role of the CD44/HA pathway in the regulation of both normal HSC-niche cross-talk and hematopoietic recovery following chemotherapy. Identification of biologically active HA polymers will provide a basis for further pre-clinical studies and may potentially lead to a development of new strategies for post-chemotherapeutical recovery of bone marrow hematopoiesis in patients.

References

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